Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REPLY: What Is the True Prevalence of Hypertrophic Cardiomyopathy?

We thank Dr. Baudhuin and colleagues for their letter regarding our recent article (1). They raise the very important and topical issue of DNA variant classification in determining whether a genetic finding is pathogenic, benign, or a variant of uncertain significance (VUS). As Dr. Baudhuin and colleagues would be aware, major international initiatives are being established to develop robust and reliable classification criteria to determine the pathogenicity of DNA variants in hypertrophic cardiomyopathy (HCM), and indeed all other cardiovascular genetic diseases. Such classification systems and variant interpretation need to take into account rapidly evolving human genetic databases such as the Exome Aggregation Consortium (ExAC), 1000 Genomes Project, Exome Variant Server (ESV), and most recently, the Genomics England 100,000 Genomes Project, as well as in silico tools (such as polyphen2 and SIFT), functional data, and cosegregation studies in families.

Significantly, the final outcome of the genetic evaluation is "probabilistic," that is, it is not a "yes/no" answer but rather a probability that the variant identified causes disease on the basis of the available supporting evidence (2,3). Dr. Baudhuin and colleagues correctly point out that over time, variant classifications can change due to new information, and this can change the classification from pathogenic to VUS or benign, and alternatively from VUS to pathogenic. We agree that this is a product of the rapid escalation of available genetic information due to newer, faster, and cheaper sequencing technologies, and highlights the importance of periodic re-evaluation of all variants. In HCM, we have previously reported that reclassification is required in up to 10% of families with HCM (4). Furthermore, the issues surrounding variant classification highlight the urgent need to have organized collaborative international efforts to curate all human disease genes and to develop classification systems directly relevant to cardiovascular disease. The recently published American College of Medical Genetics and Genomics guidelines are an important first step in this process, but need significant adaptation and modification for such guidelines to be reliable and accurate in the specific interpretation of variants relevant to cardiovascular disease. To this end, the recently developed National Institutes of Health-funded Clinical Genome Resource (ClinGen) initiative provides the hope of improving genomic interpretation by a coordinated international effort from both clinical and research communities, with the key goals to share data, build knowledge, develop and refine variant classification, and improve care.

Importantly, the revised estimated prevalence of HCM of up to 1 in 200 people is on the basis of several factors in addition to the rate of pathogenic mutations in what are known as highly intolerant sarcomere genes. Advanced imaging techniques with high-resolution cardiovascular magnetic resonance provide more reliable diagnosis by identifying left ventricular hypertrophy not appreciated with echocardiography, expanded recognition of the genotype-positive, phenotype-negative subset, while more comprehensive family-based clinical and genetic surveillance and higher clinical index of suspicion is resulting in more asymptomatic patients being identified with HCM (Central Illustration in Semsarian et al. [1]). Taking together all of these considerations, HCM appears more prevalent than current estimates, promoting greater visibility for the disease, enhancing diagnosis and consideration of contemporary treatment options (5), and ultimately improving care and outcomes in patients and families with HCM worldwide.

Christopher Semsarian, MBBS, PhD, MPH
Jodie Ingles, GradDipGenCOuns, PhD, MPH
Martin S. Maron, MD
***Barry J. Maron, MD**

*Minneapolis Heart Institute Foundation
920 East 28th Street
Suite 620
Minneapolis, Minnesota 55407
E-mail: hcm.maron@mhif.org

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Hospitalizations for Endocarditis in the United States

The paper by Pant et al. (1) and the editorial by Dayer and Thornhill (2) provided further insight into the recent pattern of endocarditis hospitalizations in the United States, and the potential causes behind the changes. However, we have several concerns about the paper and the associated editorial. Whereas Pant et al. (1) declared, "There is scant data on IE trends since this major practice change in the United States," we had published an article in the *Journal* on the same topic in 2013 (3), which was unfortunately missed by Pant et al.

Further, Pant et al. (1) provided subgroup results stratified by the potential causative organisms. However, although potentially interesting, the limitations of this analysis need highlighting. As appropriately indicated by Dayer and Thornhill (2), the codes used by Pant et al. (1) are likely inadequate for diagnosing organisms. Although using discharge diagnosis codes for endocarditis has been previously validated against the Duke criteria (4,5), we are unaware of validation studies for organism codes used by Pant et al. (1). Whereas they show an increase in staphylococcal and streptococcal endocarditis, it is unclear whether it is due to better diagnostics, change in the coding patterns, double counting the same patients, a real surge in disease occurrence, or a mix of these. The fact that there has been an increase in gram-negative, staphylococcal, streptococcal, and fungal endocarditis raises our suspicion for better diagnostics, or change in coding patterns; at least as partial contributors.

We should also clarify that the study by Pant et al. (1), similar to ours, was not a study of true incidence, but one that determined the hospitalization rates. Our study is also misrepresented in the editorial by Dayer and Thornhill (2). They state: "Bikdeli et al. looked at admissions of patients older than 65 years by using Medicare inpatient Standard Analytic Files. They recorded a reduction in the absolute numbers, but no correction was made for the absolute numbers of patients enrolled in Medicare eligible for treatment." We are surprised by this comment, because as could be inferred from our paper, even the title, we had determined the trends in hospitalization *rates*, not merely number of hospitalizations.

Behnood Bikdeli, MD
Yun Wang, PhD
***Harlan M. Krumholz, MD, SM**

*Center for Outcomes Research and Evaluation (CORE)
Yale University School of Medicine
1 Church Street, Suite 200
New Haven, Connecticut 06510
E-mail: harlan.krumholz@yale.edu

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REPLY: Hospitalizations for Endocarditis in the United States

We would like to thank Dr. Bikdeli and colleagues for their interest in our paper (1). We do apologize for not citing the work by Bikdeli et al. (2) on the trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries (1). The difference in results seen in our paper from the Bikdeli et al. (2) paper could be because of differences in study population and follow-up duration. We acknowledge the potential limitation related to coding that could influence the results of our study as well as other retrospective studies done on this topic, as pointed out by Bikdeli et al. (2). Hence, the conclusions made from the observational studies should be considered as "hypothesis generating" and not a "causal relationship." Prospective studies providing insight into the impact of the guideline is indeed lacking, and we have echoed the dire need for such study, which has been emphasized in the accompanying editorial by Dayer and Thornhill (3). Nonetheless, a common